F TENT COOPERATION TREA

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB2004/003295	08.10.2004	08.10.2003

International Patent Classification (IPC) or both national classification and IPC
A61K9/20, A61K9/28, A61K31/00

Applicant
RANBAXY LABORATORIES LIMITED

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Telephone No. +49 89 2399-

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/IB2004/003295

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

   see separate sheet

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 33-34

because:

☒ the said international application, or the said claims Nos. 33-34 regarding industrial applicability relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-34
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-34
Industrial applicability (IA)	Yes:	Claims	1-32
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Re Item I.

1) Although claims 1,13 and 32, directed to a product claim, have been drafted as separate independent claims. They appear to relate effectively to the same subject-matter, namely a composition, and to differ from each other only with regard to the definition of the subject-matter for which protection is sought and in respect of the terminology used for the features of that subject-matter. The aforementioned claims therefore lack conciseness. Moreover, lack of clarity of the claims as a whole arises, since the plurality of independent claims makes it difficult, if not impossible, to determine the matter for which protection is sought, and **places an undue burden** on others seeking to establish the extent of the protection.

   Hence, **claims 1,13 and 32** do not meet the requirements of Article 6 PCT.

   In order to overcome this objection, it would appear appropriate to file an amended set of claims defining the relevant subject-matter in terms of a single claim in each category followed by dependent claims covering features which are merely optional (Rule 6.4 PCT). Applicant should take care however not to add subject-matter which extends beyond the content of the application (Art. 19/34 PCT).

   Failure to do so or to give convincing argumentations might lead to the substantive examination of only the first independent claim and its apending claims, and to the raise of a non-unity objection as the common concept (= composition comprising paroxetine, microcrystalline cellulose, prepared by wet granulation technique) between the compositions of claims 1,13 and 32 is not novel nor inventive over prior art.

   This applies to **independent process claims 29 and 30** which can be brought together into one independent process claim.
   Furthermore **claims 33-34** could and should be made dependent from claim 1.

2) The documents cited in the International Search Report (ISR) were numbered respectively from D1-D5; this numbering results from the citation order in the ISR and will be used for the procedure. Unless otherwise specified, **the cited passages of**

each document in the ISR will be considered.

D1: WO 2004/058229 A (BIOVAIL LABORATORIES INC; MAES, PAUL, JOSE; MUHURI, GOUTAM) 15 July 2004 (2004-07-15)
D2: WO 02/069969 A (A/S GEA FARMACEUTISK FABRIK; FELUMB, NIELS, CHRISTIAN; HENRIKSEN, KRIS) 12 September 2002 (2002-09-12)
D3: WO 03/057151 A (TEVA PHARMACEUTICAL INDUSTRIES LTD; TEVA PHARMACEUTICALS USA, INC; FOX) 17 July 2003 (2003-07-17)
D4: WO 03/057150 A (TEVA PHARMACEUTICAL INDUSTRIES LTD; TEVA PHARMACEUTICALS USA, INC; FOX) 17 July 2003 (2003-07-17)
D5: WO 02/055062 A (SYNTHON B.V; PETERS, THEODORUS, HENDRICUS, ANTONIUS; VAN DALEN, FRANS;) 18 July 2002 (2002-07-18)

Re Item II.

2) For the present examination it would be assumed that the priority date of present application is valid so that the P-document D1 which falls under the definition of Rule 70.10 PCT is not considered for the PCT phase. However the applicant's attention is drawn with the fact that Document D1 will be relevant for the European Regional Phase with regard to **novelty and eventually to inventive step**.
Applicant's attention is drawn with the fact that the only technique disclosed in D1 is **wet granulation**. Therefore it is implicit that the paroxetine tablet containing **MCC** (microcrystalline cellulose) and **HPMC** is obtained from granules prepared by **wet granulation technique** (see particularly Tables 41, 66-67, p.128 L.16).

Re Item III.

3) Claims 33-34 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V.
Reasoned statement with regard to novelty, inventive step; citations and explanations supporting such statement

4) Composition claims (claims 1-28,32) and its use for treating depression (claims 33-34)

4a) The subject-matter of claims 1-16,19-28,32-34 is not new in the sense of Article 33(2) PCT because D2 (or D4: see table 2) describes a tablet containing paroxetine, MCC and a modified release polymer.

Applicant's attention is drawn with the fact that a product is **not** rendered novel **merely by the fact that it is produced by means of a new process**.
A claim defining a product in terms of a process is to be construed as a claim to the product as such and the claim should preferably take the form "Product X **obtainable by** process Y", or any wording equivalent thereto, **rather than** "Product X **obtained by** process Y" or "Product X **prepared by** process Y".

4b) The subject-matter of claims 17-18 is not new in the sense of Article 33(2) PCT because D4 (see Table 2) describes a paroxetine tablet, characterized in that it contains simultaneously **MCC and HPMC**.

4c) Should the applicant renders the composition of the present application novel by pointing out the relevance a technical feature that is not described explicitly in prior art or by introducing into the claims the use of a **specific ingredient or a specific range** or whatever, inventive step would be recognized **only if he demonstrates** that **a surprising or synergetic effect** is attributed to the introduced technical feature that the skilled man in the art could not deduct from the prior art.

In the absence of a surprising effect in comparison with prior art, inventive step cannot be acknowledged because the introduced technical feature would be considered as an **obvious alternative** that the skilled man in the art would perform **routinely** in order to distinguish with prior art.

Herewith applicant's attention is drawn with the teaching of D3 which says that "povidone or HPMC is used to keep the paroxetine hydrochloride in the granulate or in the tablet substantially anhydrous" (see p.9 L.5-8).

5) Process claims 29-31

5a) The subject-matter of claims 29-31 is not new in the sense of Article 33(2) PCT because D4 (see Table 2) describes a process for manufacturing paroxetine tablet containing simultaneously **MCC and HPMC,** characterized in that granules are produced from wet granulation techique.

5b) Even if the applicant renders the **process** of the present application novel by introducing into the claims that the wet granulation is carried out by **mixtures of water and isopropyl alcohol** (for example), it will not be inventive in view of D2 alone, or combined with D3-D4.

The document D2 is regarded as being the closest prior art to the subject-matter of the process of the present application, and discloses a process for the manufacture of tablets containing paroxetine, MCC, sodium starch glycolate as modified release polymer, mannitol and copovidone (see Example).

The problem to be solved in D2 and in present application, is to provide paroxetine tablets which are stable, did not show any discolouration and have sufficient hardness after prolonged storage (see D2: p.9 L.23-24 and p.10 L.8-10), **even if** the tablets are obtained by wet granulation technique and contain MCC.

The solution proposed in D2 consists in that the granules are dried **very fast** and have a certain **moisture content**, such fast drying is achieved in a flow of heated air (see p.3 L.26-34 and claim 1).

The solution proposed in present application consists in the granulation liquid which is a mixture of water and isopropyl alcohol, instead of water alone as mentioned in D2 (see claim 1). It cannot be considered as involving an inventive step (Article 33(3) PCT) as long as the applicant does not provide with support of **experimental tests**

that the specific present granulation liquid (mixture of solvents) **does solve** the problem **even if the granules are not dried very fast or/and have a high moisture content** as suggested in D2.

In the absence of a surprising **and** improved effect in comparison with prior art D2, inventive step cannot be acknowledged because the present granulation liquid would be considered as an **obvious alternative** that the skilled man in the art would perform **routinely** in order to distinguish with prior art. It is obvious indeed that an alcoholic aqueous solution will evaporate faster than water.

5c) Should the applicant introduce into the process claim that the paroxetine granules contain furthermore **HPMC**, his attention is drawn on the teaching of D3 which says that "povidone or HPMC is used to keep the paroxetine hydrochloride in the granulate or in the tablet substantially anhydrous" (see p.9 L.5-8).

As long as the applicant does not provide a **surprising and synergetic** effect of the combined features (which is not described in prior art), inventive step cannot be acknowledged because present application would be considered as an **obvious association** of features **resulting in an obvious accumulation** of known effects (see Guidelines CIV-Annex 2., 2.1).

6) Any information the applicant may wish to submit concerning the subject-matter of the invention, for example further details of its advantages or of the problem it solves, and for which there is no basis in the application as filed, should be confined to the letter of reply and not be incorporated into the application.

For the regional phase:

Re Item VII.

7) For the assessment of the present claims 33-34 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to

the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

8) Contrary to the requirements of Rule 5.1(a)(ii) PCT, it seems that the relevant background art disclosed in the documents D1 and D2 is not mentioned in the description, nor are these documents identified therein.

9) The attention of the applicant is drawn to the fact that the application may not be amended in such a way that it contains subject-matter which extends beyond the content of the application as filed.

In order to facilitate the examination of the conformity of the amended application with the requirements of Article 34(2)(b) PCT, the applicant is requested to clearly identify the amendments carried out, no matter whether they concern amendments by addition, replacement or deletion, and to indicate the passages of the application as filed on which these amendments are based (see also Rule 66.8(a) PCT). Preferably these indications should be submitted in handwritten form on a copy of the relevant parts of the application as filed.

10) The applicant is kindly requested to take account of the above objections and **give convincing argumentations**.
Should the applicant regard some particular matter as patentable, an independent claim should be filed taking account of Rule 6.3(b) (i), (ii) PCT (two part form claim). The applicant should also indicate in the letter of reply the difference of the subject-matter of the new claim vis-à-vis the state of the art and the significance thereof.